

**REMARKS**

Reconsideration and withdrawal of the rejections of the application are requested in view of these amendments and remarks, which place the application into condition for allowance.

Applicants thank the Examiner for suggesting an alternative title for the application.

**I. STATUS OF CLAIMS AND FORMAL MATTERS**

Claims 21-30 and 33-38 are under consideration in this application. Claims 1-7, 9, 11, 13, and 15-20 are cancelled, claims 33-38 are newly added, and claims 21-28 and 30 are amended.

Support for the recitation of “(i) contacting a cell with a modulator of Notch signaling to modify cytokine expression in the cell” in claims 21-23, 27, and 28 can be found in original claim 1. Also, support for the recitation of “cells of the immune system” in claims 21-23, 25-28, 33, and 34 can be found, for instance, on page 52, line 17 - page 54, line 7. Support for the amendment to claims 25 and 26 can be found in original claim 1. Further, support for new claims 33-37 can be found in original claims 21-24 and 27, respectively, as well as in original claim 1. Finally, support for new claim 38 can be found in original claim 30.

The specification was amended to recite a new title for the application, to add to the description of the Figures 4-30, and to remove a hyperlink. Support for the amended description of the Figures can be found throughout the specification and figures, as outlined in the table below:

<u>Amended Figure Descriptions</u>	<u>Support in the Specification</u>
Description of Figure 4	Examples 2 and 3, and Figure 4
Description of Figure 5	Examples 2 and 6-8, and Figure 5
Description of Figure 6	Example 8 and Figure 6
Description of Figure 7	Example 3
Description of Figure 8	Example 4
Description of Figure 9	Example 5
Description of Figure 10	Example 6
Description of Figure 11	Example 7
Description of Figures 12A-12D	Example 8

Description of Figure 13	Example 10
Description of Figures 14A and 14B	Example 11 and Figures 14A and 14B
Description of Figures 15A and 15B	Example 11 and Figures 15A and 15B
Description of Figure 16	Example 11 and Figure 16
Description of Figure 17	Example 11 and Figure 17
Description of Figure 18	Example 11 and Figure 18
Description of Figure 19	Example 12
Description of Figures 20A and 20B	Example 13 and Figures 20A and 20B
Description of Figure 21	Example 14
Description of Figures 22A and 22B	Example 15
Description of Figure 23	Example 15 and Figure 23
Description of Figures 24A and 24B	Example 15
Description of Figures 25A and 25B	Example 15 and Figures 25A and 25B
Description of Figures 26A-26C	Example 15 and Figures 26A-26C
Description of Figure 27	Example 16
Description of Figure 28	Example 16
Description of Figure 29	Example 17
Description of Figure 30	Example 18

No new matter is added

The claims are patentably distinct over the prior art and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendments to the claims are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but simply for clarification and to round out the scope of protection to which Applicants are entitled.

### **Priority**

Applicants note that certified copies of GB Patent Application Nos. 0118153.6, 0207930.9, 0212282.8, and 0212283.6 were filed on March 18, 2008, thereby perfecting Applicants' claim to foreign priority under 35 U.S.C. § 119.

### **Objection to the Specification**

The specification was objected to for allegedly reciting a non-descriptive title, for not providing an adequate description of Figures 4-30 in the Brief Description of the Drawings, and for containing an embedded hyperlink. These objections are addressed by the amendment to the specification as described above. Accordingly, reconsideration and withdrawal of the objection to the specification are requested.

### **Objection to the Claims**

Claims 2-7, 9, 11, 13, 17-22, 24, and 27-30 were objected to for reciting acronyms without first defining what the acronyms represent. In response, Applicants amend the claims to properly define the recited acronyms. Accordingly, reconsideration and withdrawal of the objection to the claims are requested.

## **II. THE REJECTIONS UNDER 35 U.S.C. § 112 ARE OVERCOME**

### **Indefiniteness**

Claims 1-7, 9, 11, 13, and 15-30 were rejected under the second paragraph of Section 112 as allegedly being indefinite for failing to distinctly claim the invention.

The Office Action contended that claims 1-7, 9, 11, 13, and 15-30 do not have a step that clearly relates back to the preamble, and that the recitation of “an immune modulatory cytokine profile” in claims 17-20 was unclear. The Office Action also alleged that claim 30 recites an improper Markush group. These rejections are believed to be overcome by the claim amendments presented herein.

Additionally, the Office Action alleged that the term “EGF-like” in claim 29 is allegedly indefinite. In response, Applicants assert that the specification suitably discloses the meaning of the term “EGF-like,” for example, on page 39, line 24 - page 41, line 33.

The Office Action asserted that there is insufficient antecedent basis for the term “EGF domain” in claim 30. Applicants amend claim 30 to recite “EGF-like domain” instead of “EGF domain.”

The Office Action further contended that claim 22 is indefinite because it is not clear what patient population or condition requires the reduction of a TH1 immune response. Applicants assert that the specification describes autoimmune diseases that are known to be mediated by a TH1 immune response, such as on page 87, line 1 - page 90, line 18.

Finally, the Office Action alleged that claim 27 is indefinite because it is not clear what diseases are associated with excessive TNF $\alpha$  production, IL-5 production, or IL-13 production. As a response, Applicants argue that it is well within the knowledge of one skilled in this field which diseases are associated with excessive TNF $\alpha$  production, IL-5 production, or IL-13 production. Further, one skilled in the art could readily determine whether a person had any of these diseases using the assays for the cytokines which are disclosed in Examples.

### **Enablement**

Claims 21-27 were rejected under the first paragraph of Section 112 as allegedly lacking enablement. The Examiner contended that a large quantity of experimentation is necessary to administer Notch modulators to reduce a TH2 or TH1 immune response, to treat an inflammatory or autoimmune response, or to treat a disease associated with excessive production of TNF $\alpha$ , IL-5, or IL-13. The rejection is traversed.

In response, Applicants argue that the present invention is indeed enabled and that one of ordinary skill in the art can perform the method of the present invention without undue experimentation. Applicants draw attention to the claim amendments, which clarify the invention and modify the scope of the claims. For example, the cells of the claims are recited as being cells of the immune system, which are amply described in the specification, notably on page 52, line 17 - page 54, line 7. Consequently, the claimed invention does not relate to any cell as alleged by the Office Action. Hence, in consideration of the revised scope of the instant claims, the skilled artisan would not be subjected to undue experimentation to practice the present invention.

In addition, the specification also provides substantial guidance for performing the claimed methods of the invention. For example, the specification describes screening assays, including both protein and nucleic acid assays, for determining modulators of Notch signaling on page 34, line 5 – page 35, line 27, and on page 65, line 19 – page 66, line 19. Moreover, the specification discloses cytokines which experience modified expression (page 29, line 30 – page 30, line 13; page 81, line 12 – page 84, line 6), and describes administration of both modulators of Notch signaling (page 90, line 20 – page 91, line 33) and cells of the invention (page 92, lines 2-32). Furthermore, the working examples, especially Example 5, demonstrate how the methods

of the invention can be applied to modify cytokine expression in cells. Clearly, the skilled artisan can apply these teachings to reducing TH1- and TH2-mediated immune responses.

Applicants submit that a skilled person would appreciate from the description and from the results of the experiments in the Examples how to perform the steps of modifying cytokine expression *in vivo*, *ex vivo*, and *in vitro*. While the experiments were performed using mouse and human CD4+ cells, mouse CD4+ TH1 and TH2 polarised cells and cell lines, the skilled artisan would appreciate from the specification, notably page 93, line 1 – page 94, line 19, how to modify the cells for the claimed methods.

Applicants additionally point out that, according to MPEP Section 2164.06, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)) One skilled in the art can determine the dosages and routes of administration without undue experimentation as such work is routine, especially in light of the guidance provided in the specification. Similarly, the skilled artisan can apply the teachings of the modulators of Notch signaling, the cytokines, etc., in the specification to perform the steps of the invention. Therefore, the instant claims are enabled by the specification.

### **Written Description**

Claims 1-7, 9, 11, 13, and 15-30 were rejected under the first paragraph of Section 112 as allegedly lacking adequate written description. The rejection is traversed.

Applicants disagree with the Office Action's allegation that the specification does not identify specific modulators or activators of Notch signaling, and that a skilled artisan cannot envision the Notch modulators or activators of the invention. Initially, Applicants point out that the instant claims are directed to modulators - not activators - of Notch signaling; thus, the Office Action's contention that activators of Notch signaling are not amply described is rendered moot.

Applicants assert that the specification sufficiently describes the genus of modulators of Notch signalling recited in the instant claims. For instance, the specification discloses "candidate" modulators of Notch signaling (see page 17, line 19 - page 20, line 33), as well modulators which function as antagonists (page 21, line 3 - page 22, line 32) and agonists (page 23, line 1 - page 25, line 32). Moreover, in the case in which the modulator is a Notch ligand or

a polynucleotide encoding a Notch ligand, the specification provides substantial description of Notch ligands, including domain locations and amino acid sequences associated with the domains (pages 36-41). In addition, the working examples demonstrate the use of Notch ligand mouse Delta 1 extracellular domain/Ig4Fc fusion protein (see Examples 2, 4, 6, 10, and 14). Thus, in contrast to the Office Action's contention, a skilled artisan can indeed envision the Notch modulators of the invention in light of the substantial description of such modulators provided in the specification.

Accordingly, Applicants assert that the present invention is in compliance with the requirements under Section 112 regarding definiteness, enablement, and written description. Reconsideration and withdrawal of all Section 112 rejections are requested.

### **III. THE DOUBLE PATENTING REJECTIONS ARE PROVISIONAL**

Claim 1, 15, 16-20, and 28-30 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-8, and 11-16 of copending U.S. Application Serial No. 11/178,724. Also, claims 22, 23, and 27 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending U.S. Application Serial No. 11/071,796.

Applicants point out that claims 1, 15, 16-20 are cancelled, thereby rendering their provisional rejection moot. Moreover, Applicants request that the provisional rejection of claims 22, 23, and 27-30 be held in abeyance until allowable subject matter in the present application, and the '724 application or the '796 application, are determined.

### **III. THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME**

Claims 1-7, 9, 11, 13, 15, and 17-20 were rejected under Section 102(b) as allegedly being anticipated by Gehring *et al.* (WO 01/03743). Applicant note that these claims are cancelled, thereby obviating their rejection. Accordingly, reconsideration and withdrawal of the Section 102 rejection is requested.

**CONCLUSION**

This application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

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